Discussion

Dr Michael Mulligan (*Seattle, Wash*). I would like to thank the association for inviting me to discuss this paper and Dr Khan and his colleagues for sending me the manuscript in advance. Congratulations on a fine presentation and for conducting a prospective randomized trial in an attempt to answer a timely question. You added 50% more patients between submission of the abstract and the manuscript, so I paid attention and I think I understand your take-home message but let's work through this.

I have 2 comments and then 3 questions.

The first comment is that you combined heart and lung transplant patients and I do not think that is appropriate. That is apples and oranges, and I think you think so, too, because you use different entrance criteria to include heart or lung transplant recipients. Whereas pulmonary artery pressures and elevations in pulmonary vascular resistance have obvious implications for outcomes in heart transplant patients with right ventricular dysfunction, elevated pulmonary artery pressures are not even used in the grading criteria for primary graft dysfunction after lung transplantation. Rather, we use P to F ratios and infiltrates.

Second comment—you raised 3 concerns about inhaled nitric oxide: the need for complex delivery systems, potential toxicities, and cost. Yet in your data and in your discussion, you realize that both inhaled nitric oxide and nebulized prostacyclin require somewhat complex delivery systems and you observed no toxicity so it really comes down to cost. If we have already spent so much, on a lung transplantation for example, I think it is best to use the best drug with the best bioavailability in the alveolar space with the best effect on ventilation perfusion matching, accepting an increase in cost that is real but only a small fraction of the overall price of the successful patient outcome. Ultimately, we still do not appear to know which agent is best.

I will move on to the questions.

First question, there were 17 patients in the abstract and 25 patients in the manuscript. The numbers are really too small to draw any definitive conclusions about efficacy in heart transplant recipients or in lung transplant recipients. Was this your target or did you stop enrollment early for some reason?

Dr Khan. We initially had a target of 100 patients. However, when we did our preliminary analysis and reviewed this with _____ we found reasonable data that we concluded the study early.

Dr Mulligan. I would challenge the fact that you hit a home run because hypoxia is—this is my second question. Hypoxia is the undoing of a lung transplant recipient in primary graft dysfunction; yet, in your manuscript you showed no improvement in P to F ratios with either nebulized prostacyclin or inhaled nitric oxide. Many other studies have shown beneficial effects with both. This is especially true with inhaled nitric oxide, presumably related to the better alveolar distribution of a gas as compared with a nebulized solution. Why do you suppose that in your study you did not see any improvement in P to F ratios? Did it have something to do with the 8 additional patients added, because in your abstract you did see a benefit, or was it because you simply did not have enough acute graft dysfunction in lung transplant population?

Dr Khan. The difference between the data in the abstract and the manuscript with the larger numbers, the small difference in improvement in PF ratio became no longer significant. That was because in the group of patients that had a PF ratio of less than 200, when you looked at that subgroup, they had approximately 50% increase in PF ratio because their PF ratio started in the 50–100 range. However, when you look at the mean of the whole group, the average is 200–250. When we did look at that group separately, they did have an improvement in oxygenation from both agents. However, when we added more patients, none of whom had hypoxia, it diluted out that finding.

Dr Mulligan. I think that gets back to the original comment that we probably should not mix heart and lung transplant patients together in such a study and we should expand it to include more lung transplant patients.

The last question is that in your manuscript and in your presentation you talked about a 5.3% incidence of grade III primary graft dysfunction in your lung recipients, yet 5 of 17 or 5 of 25 had P to F ratios of less than 200, which would imply a grade III primary graft dysfunction if they were lung transplant recipients. What was your actual incidence of primary graft dysfunction in this population?

Dr Khan. It was 5.3% at 48 hours. However, that initial data of the 5 patients who had hypoxemia initially was at the time of randomization in the operating room, so several of these patients improved during the next 48 hours such that there was only 1 patient remaining who met the criteria.

Dr Mulligan. There is an upfront and then there is a delayed assessment, so I do not know which one is valid but it appeared to be disparate between your early and late assessments.

Again congratulations and I appreciate the opportunity to discuss the paper.

Dr Khan. Thank you.